

# Cardiac and renal function in patients with type 2 diabetes who have chronic kidney disease: potential effects of bardoxolone methyl

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**Abstract:** The intracellular and tissue balance of oxidant and antioxidant forces is a potential therapeutic target for a variety of agents in the treatment of complications due to chronic disease including diabetes mellitus and hypertension. There are a myriad of processes controlled at the level of genes, transcription factors, and protein messages that work to control the normal use of oxidative reactions within cells. Loss of control of these processes may lead to reversible dysfunction in many cell lines including the podocyte, renal tubular cells, and cardiac myocytes. Bardoxolone methyl is a novel nuclear regulator factor (Nrf-2) activator which works to tip the balance of effects towards antioxidation and as an observation made serendipitously, improves renal filtration function in humans after approximately 12 weeks of therapy. The improvement in estimated glomerular filtration can be up to 30% in those with stage 3 and 4 chronic kidney disease. However, experimental evidence suggests there may be a consequence of relative hyperfiltration in diseased kidneys as well as potential adverse effects on skeletal and cardiac myocytes. Only large, prospective randomized trials with carefully collected and adjudicated clinical outcomes will inform the research community on the therapeutic risks and benefits of this important new agent.

**Keywords:** bardoxolone methyl, chronic kidney disease, diabetes mellitus, glomerular filtration, cardiomyocyte, oxidative stress

## Introduction

The pandemic of type 2 diabetes mellitus (T2DM) and cardiometabolic risk has led to concerns over the future population burden of chronic heart and kidney disease. Because of the very tight relationships between heart and kidney regulation, function, and codependence, changes in the operational parameters of one organ system affect the other on a multitude of levels. There has been considerable progress in the areas of preventive cardiology including smoking cessation, lipid reduction, and blood pressure and glycemic control which have resulted in reductions of myocardial infarction and heart failure; however, patients with chronic kidney disease (CKD) remain as a concern given the narrow therapeutic window for most management strategies including procedures, devices, and medications.<sup>1</sup> For example, in patients admitted with acute decompensated heart failure, approximately 25% develop type 1 cardiorenal syndrome and a sequential decline in renal filtration function which prolongs hospitalization, complicates management, and in some cases, leads to death.<sup>2</sup> Conversely, in patients with CKD, death from cardiac causes is a larger clinical threat than the development of end-stage renal disease requiring renal replacement therapy.<sup>3</sup> While conventional cardiac and renal therapeutic targets are of principal concern to

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practitioners today, the search for common cellular processes that may serve as therapeutic targets has led to promising new approaches.<sup>4</sup> Thus, the interest and enthusiasm for new therapeutic agents that can favorably affect the function of one or both organs and lead to considerable improvement in measurable clinical outcomes is piqued in this renaissance era of cardiorenal medicine.<sup>5</sup>

## The glomerular filtration barrier

The filtration barrier within the renal glomerulus has been the subject of investigation for decades. As blood moves from the renal arterioles into the preglomerular afferents and the tortuous glomerular tufts, a critical hydrostatic and oncotic pressure head is maintained.<sup>6</sup> The filtration barrier from endovascular to urinary that is traversed by water and solute includes the negatively charged endothelial glycocalyx, fenestrated endothelium, gelatinous basement membrane, and slit diaphragm created by the foot processes of podocytes. Pathobiologic changes occur at the level of the endothelium and the podocyte in all patients with T2DM that lead to the eventual decline in glomerular filtration function and loss of blood proteins in the urine; which in turn, accelerate disease progression in other nephron units and in aggregate contribute to the global development of diabetic CKD, where there is obvious histological damage to these structures in approximately two thirds of patients.<sup>7,8</sup> Thus, in patients with T2DM with optimal blood pressure and glycemic control, early preservation of normal glomerular function and use of agents that antagonize the renin–angiotensin system has been a principal approach to reducing the microvascular complications of T2DM including diabetic nephropathy. Thus, progress in the prevention or delay of the progression of diabetic nephropathy has led to the following question: what fundamental cellular pathobiologic processes can be modified to reverse dysfunction before there is cell death, loss of nephron architecture, and organ fibrosis?

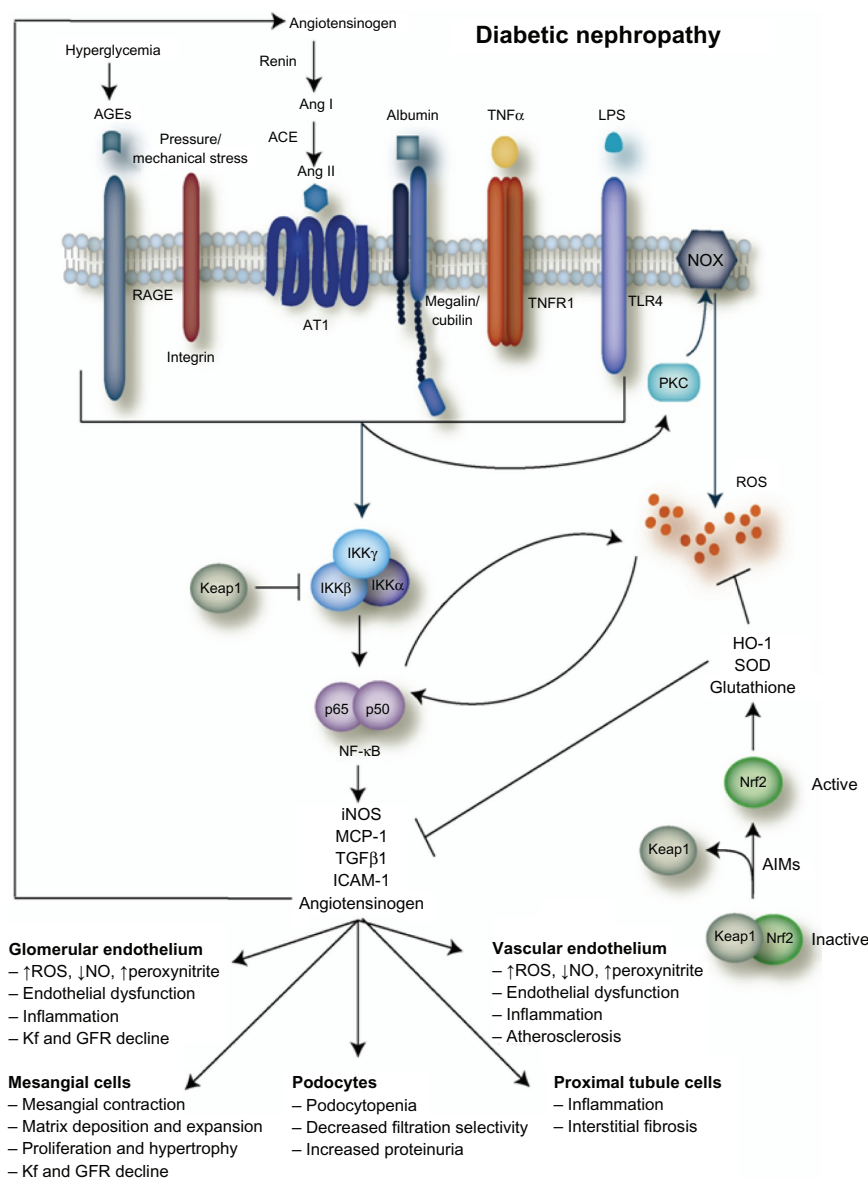
## Cell signaling and loss of metabolic control of oxidative stress

All cells in the body have fundamental metabolic functions for energy production and utilization, respiration, protein synthesis, storage, communication, and defense. Understanding of host cell defense mechanisms presumably to guard against infectious agents has led to the concept of “innate immunity.” Innate immunity means that each cell has a fundamental set of functions it can operationalize to defend a direct attack in the absence of traditional host defense systems including the traditional components of inflammation: white blood cells,

cytokines, antibodies, and complement. Mediated through a variety of conjectured mechanisms (glycated proteins, metabolic signals, insulin, adiponectin, and others), and cytokines, endothelial cells and podocytes can activate a variety of pathways used for innate immunity including intracellular production of reactive oxygen species that, in the absence of an infectious attack, work to promote cellular dysfunction and eventual death. Counter-regulation of this process offers the opportunity to reverse cellular dysfunction and potentially improve organ function. Transcription factor NF-E2-related factor 2, or Nrf-2 is a key regulator of antioxidant, anti-inflammatory and detoxification pathways within cells – presumably endothelial cells and podocytes (Figure 1).<sup>9–13</sup> In T2DM, Nrf-2 is modestly upregulated, presumably in response to the oxidative stress environment with cells. KEAP-1 (Kelch-like ECH-associated protein 1) represses the function of Nrf-2 and contributes to a regulatory balance over hundreds of genes that control oxidation/antioxidation and detoxification within cells.<sup>14,15</sup> Bardoxolone methyl (BARD) is a small molecule activator of Nrf-2, which works to push cellular metabolic balance in favor of antioxidation and detoxification and relatively overpowers KEAP-1.

## Activation of Nrf-2 by bardoxolone methyl

A variety of small molecules have been observed to activate Nrf-2. These molecules include sulforaphane derived from the cabbage family (broccoli, watercress, Brussels sprouts, cabbage and cauliflower), diallyl sulfides (from garlic, onion and chives), curcumin (from turmeric), quercetin (from tea, berries, apples and onions), astaxanthin (from krill, microalgae), resveratrol (from grapes, knotweed), and caffeic acid phenethyl ester (found in bee hives).<sup>16</sup> Of note, gold has also been shown to induce Nrf-2, and thus, may derive its anti-inflammatory properties from this mechanism. Most of the Nrf-2 activators have been shown to have some modest anti-inflammatory or antioxidant effects. Thus, the rationale for a powerful Nrf-2 activator such as BARD is supported from a broad base of molecular research. Originally tested as an anticancer agent, BARD was found to be protective against cisplatin-induced renal toxicity and improve renal filtration function in animals.<sup>17</sup> Others had found that induction of Nrf-2 by other methods also appeared to be renally protective by enhancing the cytoprotective antioxidant function of normal cells.<sup>18</sup> Thus, BARD was brought forward as a possible agent in the use of T2DM CKD where there is considerable evidence for loss of control over oxidative and inflammatory



**Figure 1** Proposed mechanisms of action of BARD on the kidney.

Adapted with permission from Ma R, Bumeister R, Stidham RD, et al, editors. Bardoxolone methyl (BARD) inhibits inflammatory signaling in cultured mesangial cells. Proceedings of the National Kidney Foundation Spring Clinical Meetings; April 13–17, 2010; Lake Buena Vista, FL.<sup>20</sup>

**Abbreviations:** AGE, advanced glycation end-product; ACE, angiotensin converting enzyme; AT, angiotensin; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; LPS, lipopolysaccharide; TLR, toll-like receptor; NOX, NADPH oxidase; PKC, protein kinase C; IKK, I $\kappa$ B kinase; KEAP, Kelch-like ECH-associated protein 1; HO, heme oxygenase; ROS, reactive oxygen species; SOD, superoxide dismutase; NF, nuclear factor; NOS, nitric oxide synthase; Nrf, nuclear regulatory factor; MCP, monocyte chemoattractant protein; TGF, transforming growth factor; ICAM, intracellular adhesion molecule; NO, nitric oxide; GFR, glomerular filtration rate.

processes within vascular and glomerular endothelial cells, podocytes, mesangial cells, and proximal tubules.<sup>19,20</sup>

## Clinical observations with bardoxolone methyl

The majority of studies evaluating BARD in humans are in abstract form and presented in Table 1. Because transcription factor-kappa B and signal transducer and activator of transcription 3 are activated in many tumors and promote proliferation, angiogenesis, metastasis, and tumor survival,

Hong and coworkers intended to leverage the KEAP-1 binding and Nrf-2 inhibition with BARD 900 mg per oral four times daily (po qd) as part of a 21 day/28 cycle treatment of multidrug chemotherapy in patients with a variety of primary cancers (melanoma, renal, thyroid, and others) for up to 12 months.<sup>21</sup> Bardoxolone methyl appeared to reduce tumor cell variability, signal transducer and activator of transcription 3, and transcription factor-kappa B expression by immunohistochemistry in subjects with repeated biopsies. In addition, the drug was well tolerated in these patients

Table 1 Selected studies in abstract or manuscript form concerning the effects of BARD

Authors	Title	Model sample	Methods	Findings
Hong <sup>21</sup>	Phase I trial with a novel orally administered synthetic triterpenoid RTA 402 (CDDO-Me) in patients with solid tumors and lymphoid malignancies	30 patients	RTA 402 administered orally from 5 mg/day to 1300 mg/day for 21 days of a 38 day cycle in an attempt to determine the MTD and DLT.	Orally administered RTA 402 was tolerated up to 900 mg/day. DLT found to be a rise in alanine aminotransferase in 2 patients.
Schwartz <sup>26</sup>	Bardoxolone, a novel oral anti-inflammatory agent improves glycemic control in T2DM with chronic kidney disease	57 patients	Bardoxolone administered orally once daily for 28 days, 60 patients randomized to each of three dose levels: 25 mg, 75 mg, and 150 mg. Primary efficacy endpoint: eGFR. CKD measured by serum creatinine, creatinine clearance, cystatin C, phosphorus, uric acid, angiotensin 2. Also measured was circulating endothelial cells HbA <sub>1c</sub> , fasting plasma glucose.	BARD improves glycemic control in patients with extensive history of T2DM and numerous co-morbidities. HbA <sub>1c</sub> decreased significantly, and fasting plasma glucose also decreased.
Schwartz <sup>25</sup>	Bardoxolone methyl improves renal function in patients with chronic kidney disease and T2DM	60 patients	Bardoxolone administered orally once daily for 28 days, 60 patients randomized to each of three dose levels: 25 mg, 75 mg, and 150 mg. Primary efficacy endpoint: eGFR. CKD measured by serum creatinine, creatinine clearance, cystatin C, phosphorus, uric acid, angiotensin 2, circulating endothelial cells, HbA <sub>1c</sub> , and fasting plasma glucose.	Phase II study indicates a beneficial effect of BARD on renal function. BARD significantly improved renal function, as measured by MDRD eGFR. Consistent improvements in creatinine clearance, cystatin C, BUN, uric acid, and phosphorus. Effects more pronounced in patients with more severe kidney impairment. Cardiovascular markers improved as well.
Pergola <sup>39</sup>	Phase IIA-bardoxolone methyl (BARD) improves renal function with stage 4 chronic kidney disease and T2DM	57 patients	BARD administered orally, once daily for 28 days, at three doses, 25 mg, 75 mg, and 150 mg. Patients are diabetics with stage 3–4 CKD.	Treatment with BARD for 28 days resulted in significant improvements in renal function. eGFR improved 10% in 25 mg group, and slightly above 30% in 75 and 125 mg groups. Improvements also found in serum creatinine clearance, cystatin C, BUN, uric acid, and phosphorus.
Agrawal <sup>17</sup>	Bardoxolone methyl is renoprotective in a rat model of cisplatin induced acute kidney injury	41 rats	Two experiments performed. Experiment 1 tested whether a low dose of BARD would protect against cisplatin induced nephrotoxicity. Rats given single dose of 2.5 mg/kg BARD a day. In experiment 2 a single dose of 10 mg/kg BARD administered on Day 1. Both experiments rats received cisplatin at 6 mg/kg on Day 0.	Experiment 1: Found slight reductions in the levels of serum creatinine and BUN in cisplatin treated animals that were not statistically significant. Experiment 2: Found significant reduction in concentration of serum creatinine (35% and 48% on day 4 and 5 respectively) relative to placebo.
Meyer <sup>22</sup>	Bardoxolone, a novel oral anti-inflammatory agent shown to improve renal function	60 patients	Compilation of 2 Phase I studies in 60 oncology patients who completed at least 21 days of therapy. BARD administered once daily for 21/28 days with accelerated dose titration starting at 5 mg/day to 1300 mg/day.	Consistent, statistically significant improvements in eGFR and serum creatinine. Mean decrease of serum creatinine of 19.3%, corresponding to a mean 20.9% increase in GFR within 21 days of BARD therapy.
Wigley <sup>40</sup>	Bardoxolone methyl activates Nrf2 and Inhibits NF-κB in renal cells	Cell cultures	Objective was to determine whether BARD induces Nrf-2 activation and suppresses inflammation in several renal cell types. Renal cell lines were treated with a range of BARD concentrations. Effects of BARD on NF-κB pathway assessed by monitoring phosphorylation and turnover of IκB by western blot and by secretion of MCP-1 by ELISA.	BARD induced expression of Nrf2 target genes in all cell lines at concentrations as low as 10 nM, thus resulting in enhanced cytoprotective antioxidant capacity in multiple cultured renal cell lines. BARD inhibits renal inflammation, evidence by inhibition of NF-κB signaling in response to TNF alpha or bovine serum albumin in multiple cultured renal cells.

Pergola <sup>41</sup>	Bardoxolone methyl (BARD) improves kidney function in patients with T2DM and chronic kidney disease	80 patients	Stratum I: 60 patients randomized to 25, 75, or 150 mg BARD for 28 days. Stratum 2: 20 patients received 25 mg per day for 28 days and then 75 mg per day for another 28 consecutive days. Objective was to determine the effects of BARD on the GFR. Secondary objective to determine safety and tolerability of BARD.	Significant dose and time dependent changes seen in eGFR. 89% of patients in each stratum showed eGFR increase. Improvements also seen in serum creatinine, creatinine clearance, BUN, phosphorus, uric acid, cystatin C, endothelial function, and inflammation.
Meyer <sup>42</sup>	Bardoxolone methyl improves markers of renal and cardiovascular outcomes in patients with T2DM and chronic kidney disease	Gene expression/ biomarker	Assessed the effect of BARD on Nrf2 activity and biomarkers of renal and cardiovascular inflammation and oxidative stress. Nrf2 target gene expression, circulating endothelial cells and levels of angiotensin I and angiotensinogen measured in vitro and in clinical samples.	BARD induces Nrf2 in CKD patients, as measured by mRNA levels of its target gene NQO1. BARD suppresses RAS signaling as measured by angiotensinogen expression. BARD significantly decreased cultured endothelial cells and measurable iNOS suggesting possibly less vascular damage via an improvement in endothelial dysfunction and a reduction in vascular inflammation.
Pergola <sup>23</sup>	Effect of bardoxolone methyl on kidney function in patients with T2DM and Stage 3b-4 CKD	20 patients	Study assessed 20 patients with moderate to severe chronic kidney disease and type 2 diabetes. Patients received 25 mg of BARD for 28 days followed by 75 mg daily for an additional 28 days.	The study found an improvement in 90% of patients' eGFR, with average increase in estimated glomerular filtration rate of 7.2 mL/min/1.73 m <sup>2</sup> .
Pergola <sup>26</sup>	Bardoxolone methyl and kidney function in CKD with type 2 diabetes	227 patients	Phase II randomized, placebo-controlled, double blind study, 227 CKD patients received placebo or bardoxolone methyl at dosage of 25 mg, 75 mg, or 150 mg once daily. Study compared GFR with placebo group versus bardoxolone group, at 24 and 52 weeks.	Results estimated eGFR improvement of 8.2 ± 1.5 mL in 25 mg group, 11.4 ± 1.5 mL in the 75 mg group, and 10.4 ± 1.5 mL in the 150 mg group. The increases in eGFR were maintained through week 52 with increase from baseline of 5.8 ± 1.8 mL, 10.5 ± 1.8 mL, and 9.3 ± 1.5 mL in the 25 mg, 75 mg, and 150 mg group, respectively.
Stidham <sup>43</sup>	Antioxidant inflammation modulators increase glucose metabolism in muscle cells	Cell culture	Investigated BARD effect on glucose metabolism in cultured skeletal muscle. Uptake of 2 deoxyglucose and GLUT4 translocation to the plasma membrane were monitored in differentiated L6 muscle cells treated with RTA405 and BARD.	BARD and its analog RTA405 increase glucose uptake and utilization into muscle cells. Treatment of muscle cells results in a dose dependent increase in glycolytic intermediates, pyruvate, and lactate. Suggests that muscle spasms may be a reflection of changes in glucose metabolism and local disturbances in pH. Also may explain better glycemic control observed in T2DM.

**Abbreviations:** BARD, bardoxolone methyl; BUN, blood urea nitrogen; CKD, chronic kidney disease; DLT, dose-limiting toxicities; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; GLUT4, glucose transporter; iNOS, inducible nitric oxide synthase; MCP, monocyte chemoattractant protein; MDRD, modification of diet in renal disease; MTD, maximum tolerated dose; NF-κB, transcription factor-kappa B; NQO1, human quinone oxidoreductase; Nrf2, NF-E2-related factor; RAS, renal artery stenosis; RTA, compounds belonging to Reata Pharmaceuticals, Inc; T2DM, type 2 diabetes mellitus.

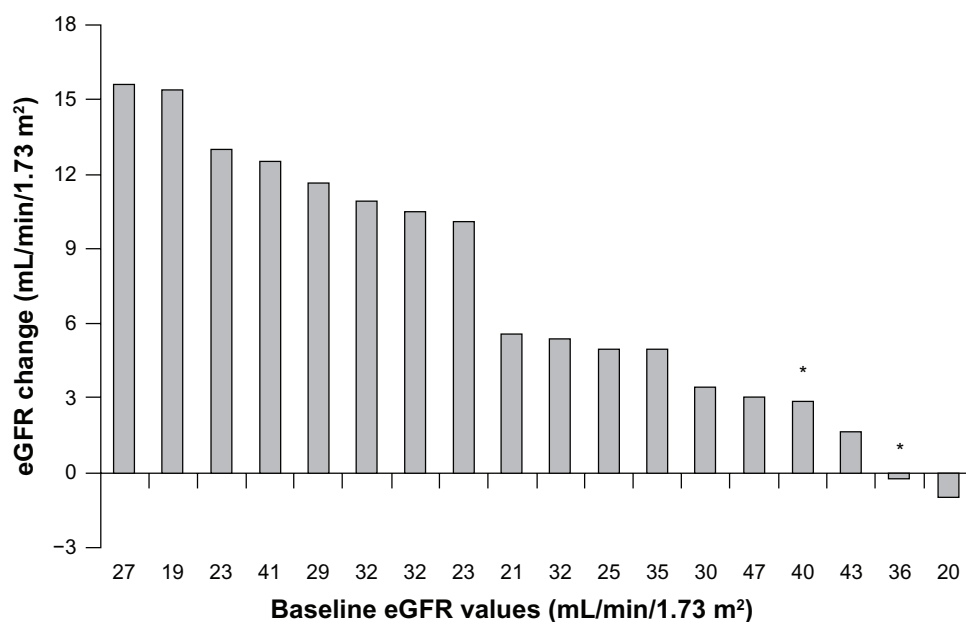


with advanced tumor burden. The first paper incorporating these patients as well as another group of Phase I subjects was presented in 2009 and demonstrated within 21 days, in patients with baseline serum creatinine levels and estimated glomerular filtration rate (eGFR) of 1.00 mg/dL and 79.9 mL/min/1.73 m<sup>2</sup>, respectively, 82% (49/60) of BARD-treated patients experienced a mean decrease in serum creatinine levels of 19.3%, corresponding to a mean 20.9% increase in eGFR. Of note, the eGFR improvements were more pronounced in a subset (n = 13) of patients with established CKD (eGFR < 60 mL/min/1.73 m<sup>2</sup> at baseline). In these patients the eGFR increased a mean of 27.6%. The changes in eGFR were sustained over six months, supported by decreases in blood urea nitrogen, and unrelated to changes in body weight.<sup>22</sup> This observation made in 2008 by Meyer and coworkers was the springboard for a new direction in product development and a Phase II trial of BARD in patients with diabetic nephropathy.

Pergola and colleagues in April 2011 published the first prospective, open-label multicenter study of BARD 25 mg po qd for 28 days and titrated to 75 mg for an additional 28 days in 20 patients with diabetic nephropathy (Figure 2).<sup>23</sup> The mean age of subjects was 64 years, average duration of T2DM was 16 years, mean eGFR was 30.3 mL/min/1.73 m<sup>2</sup>, and 45% had an albumin:creatinine ratio in the urine > 300 mg/g. At 56 weeks, the mean and median eGFR rose by 7.2 and 5.5 mL/kg/1.73 m<sup>2</sup> respectively,  $P < 0.0001$ .

Those with the lowest baseline eGFR values tended to have the greatest increases with BARD (Figure 1). Of note, there was a minor increase in 24 hour urine creatinine ( $1272.1 \pm 452.7$  to  $1333.5 \pm 440.6$ ,  $P = 0.47$ ) and an increase in a urinary marker of renal damage, neutrophil gelatinase-associated lipocalin (NGAL) from  $79.0 \pm 98.8$  to  $93.2 \pm 112.5$ ,  $P = 0.93$ . Thus, there were questions over real changes in renal filtration function and whether or not BARD influenced constitutive production of NGAL, a marker of chronic renal damage in diabetic nephropathy.<sup>24</sup> The most common adverse effect reported was skeletal muscle spasms in 35% of subjects. Of note, Schwartz and colleagues observed that glycemic control improved in patients with T2DM as given in Table 1.<sup>25</sup>

These observations were the basis for a Phase II double-blind placebo controlled trial of BARD at three doses (25, 75, 150 mg) versus placebo in 227 T2DM patients with an eGFR 20 to 45 mL/min/1.73 m<sup>2</sup> (stages 3 and 4 CKD).<sup>26</sup> The primary and secondary outcomes were the change from baseline in eGFR at 24 and 52 weeks, respectively. The mean eGFR was 32 mL/min/1.73 m<sup>2</sup>. The albumin:creatinine ratio was less than 30 (normoalbuminuria) in 37% of patients, 30 to 300 (microalbuminuria) in 29%, and more than 300 (macroalbuminuria) in 34%. The rise in eGFR for each group treated with BARD peaked at 12 weeks. The greatest mean increase in eGFR was observed in the BARD 75 mg group, 11.4 mL/min/1.73 m<sup>2</sup> from a baseline of 33.0 (36% increase). Increases in all three groups were sustained out



**Figure 2** Larger improvements in renal function human subjects with lower eGFR.

Copyright © 2011, Karger AG. Reproduced with permission from Pergola PE, Krauth M, Huff JW, et al. Effect of bardoxolone methyl on kidney function in patients with T2D and Stage 3b-4 CKD. *Am J Nephrol*. 2011;33(5):469-476.<sup>23</sup>

**Note:** Asterisks indicate patients who did not undergo successful dose escalation to 75 mg/day.

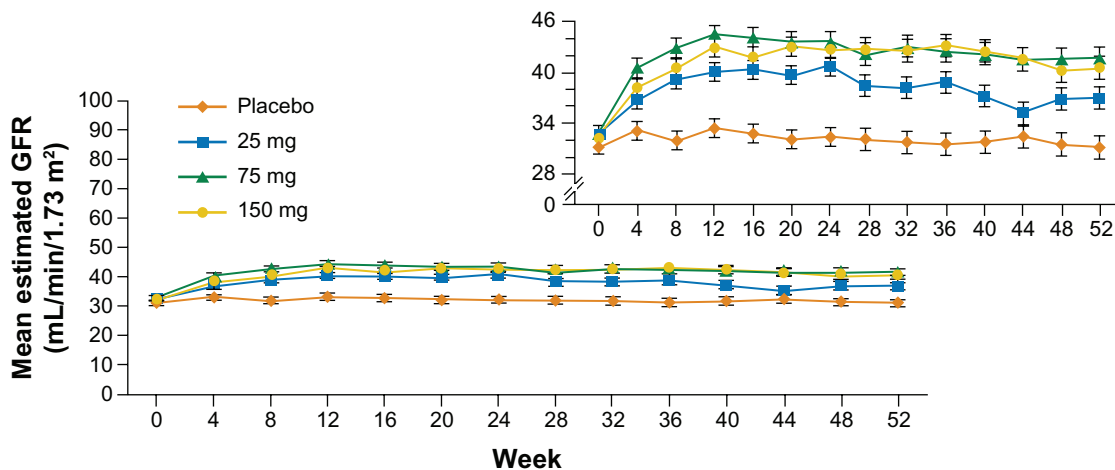
to 52 weeks (Figure 3). Again the most common adverse event reported with BARD was muscle spasms which occurred in 42% of the 25 mg group, 61% of the 75 mg group, and 59% of the 150-mg group. The muscle spasms were most common in the calf muscles of the lower leg. Additionally, hypomagnesemia occurred in 21%, 25%, and 32% of the BARD 25, 75, and 150 mg groups, respectively. A total of 18 patients (11%) had transient alanine aminotransferase elevation of more than three times the upper limit of the normal range, but there was evidence of cholestasis or hepatic failure.

The synthesis of clinical information to date with BARD on the kidneys is mixed. While there is improvement in eGFR, elimination of urinary creatinine was not impressive and there was no salutary signal seen with NGAL, a reliable proteomic measure of renal health both in chronic and acute kidney disease.<sup>27</sup> There have been no studies on the influence of BARD on microalbuminuria or proteinuria. Because BARD has been associated with a reduction in body weight, of which ~25% is usually muscle mass, it is possible that a portion of the improvement in eGFR is attributable to a reduction in creatinine production.<sup>28</sup> While BARD may improve renal filtration by a variety of effects on the filtration barrier, it is possible that it also has a hemodynamic effect and result in elevation of intraglomerular pressure. As a

result of either mechanism, there is considerable translational evidence that increasing glomerular filtration in the setting of a reduced nephron mass is due to hyperfiltration of the remaining nephrons. Hyperfiltration, while in the short-term lowers serum creatinine, ultimately leads to greater losses of nephrons and ultimately a hastened progression of kidney disease in many models.<sup>29</sup>

### Potential effects of bardoxolone methyl and the cardiomyocyte

As with potential salutary effects on the podocyte and other participating line lines involved in glomerular filtration, it is possible that BARD may impact the myocardium. The consistent effect of BARD on skeletal muscle suggests it influences either transit of electrolytes across the cell membrane and sarcoplasmic reticulum or contractile elements more directly as a result of its many influences on the nucleus. Lower blood magnesium levels are common with BARD and it is possible that a relative deficiency of cellular and plasma magnesium could lead to myocyte and dysfunction and arrhythmias.<sup>30,31</sup> In addition, hypomagnesemia has been associated with renal tubular inflammation via activation of nuclear factor kappa beta and a more progressive course to end-stage renal disease in patients with diabetic nephropathy.<sup>32,33</sup> It has been shown that Nrf-2 upregulates the mRNA, protein, and activity of



**No at risk**

Placebo	57	56	55	53	54	54	54	53	53	52	53	51	53	52
Bardoxolone methyl, 25 mg	57	53	52	52	52	51	51	49	49	47	48	48	48	48
Bardoxolone methyl, 75 mg	57	55	51	51	53	52	52	51	48	50	50	48	48	48
Bardoxolone methyl, 150 mg	56	55	55	54	53	52	52	48	48	47	47	46	46	44

**Figure 3** Overall changes in eGFR with three dose levels of BARD. Copyright© 2011, Karger AG. Reproduced with permission from Pergola PE, Krauth M, Huff JW, et al. Effect of bardoxolone methyl on kidney function in patients with T2D and Stage 3b-4 CKD. *Am J Nephrol.* 2011;33(5):469-476.<sup>23</sup>

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the antioxidant enzyme heme-oxygenase-1 as well as mRNA and protein for nuclear respiratory factor-1 (Nrf-1) in cardiac myocytes.<sup>34</sup> Heme-oxygenase-1 directs a feedback loop involving the generation of intracellular carbon monoxide and hydrogen peroxide to amplify the expression of the gene for Nrf-1 and the accumulation of nuclear Nrf-1 protein leads to gene activation for mitochondrial biogenesis, which opposes apoptosis and necrosis in experimental models anthracycline-induced cardiac injury. However, mitochondrial biogenesis can also be induced by peroxisome proliferator-activated receptor (PPAR) gamma co-activator-1 alpha.<sup>35</sup>

In both animal models and clinical trials, stimulation of PPAR-gamma therapeutically over time leads to salt and water retention and heart failure.<sup>36</sup> Changes in myocyte mitochondrial biogenesis may link future observations with BARD in both the skeletal muscles and the heart. Thus, a biphasic response can be seen with early improvement and later decline reflected by the increase and later decrease in the number of mitochondria within the cells.<sup>37</sup> We recognize this line of deduction concerning intracellular processes and the effects of BARD is highly speculative at this point, however, if blood pressure is found to increase or if impaired left ventricular function is observed in future trials with BARD, this chain of logic should be considered. In summary, BARD could induce overall favorable effects on the heart via its improvement in eGFR; however, at a cellular and tissue level, chronic exposure to BARD theoretically could lead to adverse changes that contribute either directly or indirectly to cardiomyopathy, pump failure, and arrhythmias.

## Summary

This review has summarized the cellular and clinical effects of BARD to date as they relate to the heart and kidneys. While there is great hope for an agent that improves renal filtration function, we reserve caution with respect to adverse organ toxicity over time to both the glomerulus and the myocardium. Only large, prospective randomized trials with carefully collected and adjudicated clinical outcomes will inform the research community on the therapeutic risks and benefits of this important new agent.

## Disclosure

The authors report no conflicts of interest in this work.

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